

10/624419 10/20/03

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 October 2001 (11.10.2001)

PCT

(10) International Publication Number
WO 01/74343 A2

(51) International Patent Classification⁷: A61K 31/00

(21) International Application Number: PCT/US01/10291

(22) International Filing Date: 30 March 2001 (30.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/193,120 30 March 2000 (30.03.2000) US
09/820,420 29 March 2001 (29.03.2001) US

(71) Applicant: 3M INNOVATIVE PROPERTIES COMPANY [US/US]; 3M Center, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(72) Inventor: SLADE, Herbert B.; Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(74) Agents: HOWARD, Mary Susan et al.; Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/74343 A2

(54) Title: METHOD FOR THE TREATMENT OF DERMAL LESIONS CAUSED BY ENVENOMATION

(57) Abstract: A method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion is disclosed.

**Meth d for the Treatment of Dermal Lesions
Caused by Envenomation**

Field of the Invention

5 The present invention relates to methods for treating dermal lesions caused by envenomation. In particular the present invention relates to a method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines,

10 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion.. The present invention also provides a method of preventing dermonecrosis caused by envenomation comprising applying a

15 therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged

20 imidazoquinoline amines to the site of the envenomation.

Background of the Invention

Many imidazoquinoline amine, imidazopyridine amine, 6,7-fused cycloalkylimidazopyridine amine, imidazonaphthyridine amine, tetrahydroimidazonaphthyridine amine, oxazolopyridine amine, oxazoloquinoline amine, thiazolopyridine amine, thiazoloquinoline amine and 1,2-bridged imidazoquinoline amine immune response modifiers are known. These compounds are hereinafter sometimes referred to as immune response modifying compounds (IRMs). Such compounds, methods for preparing them, formulations containing them and methods of using them are disclosed in, for example, U.S. Patent Nos. 4,689,338; 5,389,640; 5,268,376; 4,929,624; 5,266,575; 5,352,784; 5,494,916; 5,482,936; 5,395,937; 5,238,944; 5,175,296; 5,693,811; 5,741,908; 5,756,747; 5,939,090; 6,110,929; 4,988,815; 5,376,076; 6,083,505; 6,039,969;

and PCT Publications WO 99/29693, WO 00/40228, WO 00/76505, WO 00/76518 and WO 00/76518.

5 The IRM compounds have demonstrated antiviral and antitumor activity. The antiviral and antitumor activity is not direct but is believed to result from their ability to stimulate an innate immune response. In cultures of human peripheral blood mononuclear cells, members of this class of compounds have been shown to stimulate the production and release of a variety of cytokines and chemokines including interferon- α , tumor necrosis factor- α , interleukin-1 (IL-1), IL-1 receptor antagonist, IL-6, IL-8, IL-12, monocyte chemotactic protein-1 (MCP-1) and macrophage inflammatory protein (MIP-1 α).

10

15 In addition to stimulating an innate immune response, the IRM compounds have been found to mediate the acquired immune response. In human peripheral blood mononuclear cell cultures, members of this class of compounds have been shown to induce the production of the T helper type 1 (TH1) cytokine interferon- γ and to inhibit the production of T helper type 2 (TH2) cytokines IL-4 and IL-5.

20 One of these IRM compounds, known as imiquimod (1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine), has been commercialized in a topical formulation, AldaraTM cream, for the treatment of anogenital warts associated with human papillomavirus. Imiquimod is also being evaluated in clinical trials for use in treating superficial basal cell carcinoma and actinic keratosis.

Another of these IRM compounds, known as resiquimod (4-amino-2-ethoxymethyl- α,α -dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol), is being evaluated in clinical trials for use in preventing genital herpes recurrences.

25 There are numerous venomous flora and fauna in the world, some of which possess venom that causes significant medical problems when a human or an animal is exposed to the venom. Envenomation by such a plant or animal can cause both systemic and local reactions. Examples of local reactions include edema, erythema, induration, necrotic ulcers, pain, pruritis, and vesicles. The severity of the reaction is dependent on a variety of factors including the source of the venom (e.g. *Loxosceles* spider, box jellyfish, fire ant), the amount of venom injected, the location of the bite or sting (e.g. arm, thigh), and prior exposure to the venom. A variety of treatments have been used including analgesics, antibiotics, antivenoms, corticosteroids, Dapsone, and hyperbaric oxygen. In those

30

instances where the initial dermal lesion progresses to dermonecrosis, surgical intervention is often necessary. There is a continuing need for new treatments and in particular for treatments that will prevent dermonecrosis.

5

Summary of the Invention

The present invention relates to a method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion.

The present invention also provides a method of preventing dermonecrosis caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the envenomation.

20

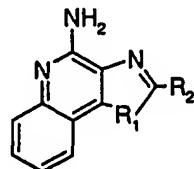
Detailed Description of the Invention

As used herein the term "envenomation" means injection of a poisonous material (venom) by sting, spine, fang, tooth, or other venom delivery apparatus.

Immune response modifier (IRM) compounds that are useful in practicing the methods of the present invention are selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines. Such compounds and methods for preparing them are disclosed in, for example, U.S. Patent Nos. 4,689,338; 5,389,640; 5,268,376; 4,929,624; 5,266,575; 5,352,784; 5,494,916; 5,482,936; 5,395,937; 5,175,296; 5,693,811; 5,741,908; 5,756,747; 6,110,929; 4,988,815; 5,376,076; 6,083,505;

6,039,969; and International Publications WO 99/29693; WO 00/76505; WO 00/76518 and WO 00/76518. The entire disclosure of each of these patents and patent applications is incorporated herein by reference.

Preferred IRM compounds for use in the practice of the methods of the invention 5 include compounds of Formula I



wherein

R₁ is selected from the group consisting of S and NR₃,

10 R₂ is selected from the group consisting of hydrogen, straight and branched chain alkyl containing one to six carbon atoms, and alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms; and

15 R₃ is selected from the group consisting of straight and branched chain alkyl containing one to six carbon atoms and straight and branched chain hydroxy alkyl containing one to six carbon atoms; or a pharmaceutically acceptable salt thereof.

Preferred R₂ groups include hydrogen, methyl, ethyl, propyl, butyl, and ethoxymethyl.

Preferred R₃ groups include 2-methylpropyl and 2-hydroxy-2-methylpropyl.

20 Particularly preferred IRM compounds include 4-amino-2-ethoxymethyl- α,α -dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol (resiquimod), 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod), 2-methylthiazolo[4,5-c]quinolin-4-amine, 2-ethylthiazolo[4,5-c]quinolin-4-amine, 2-propylthiazolo[4,5-c]quinolin-4-amine and 2-butylthiazolo[4,5-c]quinolin-4-amine.

25 In the method of the invention a therapeutically effective amount of the IRM compound is applied. The term "therapeutically effective amount" means an amount sufficient to induce a therapeutic effect such as the amelioration of symptoms (e.g. pain, erythema diminution of lesions,) or the prevention of dermonecrosis. The specific amount

that will constitute a therapeutically effective amount will vary according to factors readily determined by those skilled in the art including the activity of the particular IRM compound being used, the particular formulation being administered, the duration of the administration and the frequency of the administration. Generally from about 1 μ g to 5 about 125 mg, preferably from about 10 μ g to about 25 mg, of the IRM compound is applied to the dermal lesion.

Any conventional dosage form suitable for topical application may be used including creams, gels, lotions, ointments, sprays and transdermal patches. Preferred formulations include creams and gels. Suitable formulations are disclosed, for example, in 10 U.S. Patents 5,238,944 and 5,939,090 and International Publication WO 00/40228, the disclosures of which are incorporated by reference herein.

The frequency and duration of administration can vary as needed for amelioration 15 of symptoms and/or prevention of dermonecrosis. Treatment regimens may include administration from twice per day to once per week, preferably two to three times per week, for at least one week, preferably for two to three weeks.

There are many venomous creatures whose bite or sting causes local reactions in 20 humans. Examples of such creatures include, for example, arthropods such as arachnids (e.g., scorpions, spiders) and insects of the order Hymenoptera (e.g., bees, wasps, ants), and marine animals such as jellyfish, stone fish, stingrays, and blue ringed octopus. The venom of some species is known to cause dermal lesions that can progress to dermonecrosis. Examples of such species include *Loxosceles* spiders (*L. reclusa*, *L. deserta*, *L. laeta*), hobo spiders (*Tegenaria* spp), yellow sac spiders (*Cheiracanthium* spp.), fire ants (*Solenopsis invicta*), and jellyfish (*Chironex fleckeri*, *Carybdea alata*, *Cassiopea andromeda*, *Aurelia aurita*).

25 Venoms are frequently complex mixtures of a variety of substances. Substances that have been identified include enzymes e.g. phospholipases, hyaluronidases, cholinesterases; alkaloids e.g. methyl-N-piperidine; proteins e.g. melittin; and peptides. The particular constituents will depend on the source of the venom. When envenomation occurs a number of different types of epithelial and endothelial cells are exposed to the 30 venom. These cells are capable of synthesizing and releasing a wide variety of chemokines and cytokines in response to a variety of stimuli. For example, it has been shown *in vitro* that *Loxosceles deserta* venom induces endothelial and epithelial cells to

secrete both α and β chemokines. The release of chemokines and cytokines triggers additional events such as the attraction of neutrophils to the site of envenomation. While some of the local skin reactions that are manifested as a result of envenomation such as edema and erythema are caused directly by constituents of the venom due to the hemolytic action of various enzymes, it has been hypothesized that dermonecrosis may be due to an immune response.

While not wishing to be bound by theory, it is believed that effects of the IRM compound overwhelm the local physiological effects of the venom. This may occur by modifying the qualitative properties of the local soluble mediators of inflammation such that signaling for neutrophil activation and degranulation is inhibited. In addition, the early aggregation of neutrophils in dermal blood vessels may be diffused by IRM compound induced cytokines by stimulating the migration of neutrophils out of local vasculature and into surrounding tissue. Thus, if activated neutrophils are no longer aggregated in the discrete focal area of the site of envenomation, the amount of central necrosis may be inhibited. In essence, the venom induced "immune dysregulation" may be overcome by the immune stimulation provided by the IRM compound.

Example

Treatment of *Loxosceles reclusa* envenomation with Imiquimod 5% Cream

20

Background

A privatized correctional facility in Texas experienced a cluster of spider bite cases due to *L. reclusa* shortly following the receipt of a shipment of used mattresses from a local county jail. Spiders may have inhabited the mattresses when they were stored for several weeks in a dark shed out behind the facility. Following the first several cases, fumigation with a synthetic pyrethroid (PT 1200, resmethrin) was performed. While this agent is considered effective against *L. reclusa*, the spiders must generally be contacted directly, and unhatched eggs are less susceptible.

The diagnosis of loxoscelism in these cases was made by exclusion. No spiders were recovered despite the use of glue traps, although in one case, a "brown spider" dropped from the ceiling of a shower onto the breast of a female patient, who brushed the spider away after sustaining a bite. The following aspects of these cases favor a diagnosis

of *L. reclusa* envenomation: the spider is endemic to the area; the bites occurred mostly at night and were characterized by lack of immediate pain. Blanching and cyanosis slowly developed at the central core, with spreading erythema and progression to dermonecrosis. Other insects are known to inflict bites with similar clinical findings but can be excluded

5 on the grounds that they are not found in Texas (various tarantulas, Australian funnel-web spiders (*Atrax spp.*), "hobo spiders" (*Tegenaria spp.*); they form characteristic webs not found in the facility (yellow sac spiders (*Chiracanthium spp.*); black-and-yellow orb weavers (*Argiope spp.*); or they bite during the day ("jumping spider" (*Phidippus audax*)). *Phidippus* species are very aggressive and bite commonly, but they inflict only slightly

10 painful bites resulting in erythematous papules or small urticarial wheals. The only alternative suspect is *Latrodectus mactans* ("Southern black widow"). This spider is shy in behavior, similar to *L. reclusa*, and bites often go unnoticed until a red papule progresses to a larger halo or target lesion up to 2 cm in diameter. Unlike the *L. reclusa* bite however, skin manifestations are minimal. Victims are more likely to experience

15 muscle spasms and cramping within hours of envenomation, together with weakness of the legs and tightness of the chest. These clinical findings were absent in the cases reported here.

Methods

20 Patients were seen in the facility clinic on the day they complained of a painful lesion. Most patients related a history of discovering the lesion upon awakening in the morning. The treatment of the first 12 consecutive cases, occurring over a 5 month period, consisted of a single intramuscular dose of ceftriaxone 1 gm and oral dicloxicillin 500 mg bid x 10 days, plus either topical triamcinolone 0.1% applied bid, topical papain-urea-

25 chlorophyllin copper complex sodium debriding-healing ointment (PanafilTM) applied daily, or daily topical becaplermin (rh-PDGF-BB) 0.01% gel (RegranexTM). Where necessary and appropriate, patients were transported to the local University Medical Center for surgical debridement of necrotic lesions.

30 A consecutive series of 7 bites on 5 patients were treated with imiquimod 5% cream (available under the tradename ALDARA from 3M Pharmaceuticals, St. Paul, MN, USA) applied by the clinic staff, three times per week (typically Monday, Wednesday and Friday) for two weeks. Sufficient cream was used to cover the area of erythema, rubbing

the cream gently until it "vanished" as per labeled instructions. In addition, a single intramuscular dose of ceftriaxone 1 gm was given together with oral dicloxicillin, 500 mg bid for 10 days. Patients were re-examined by a physician at 7, 14 and 28 days following initiation of therapy.

5

Results

The first 12 patients, managed using conventional therapy, presented with tender to painful lesions consisting of a central core of induration and blanching, surrounded by 3-8 cm of erythema. Among these, 7 progressed to tissue necrosis within 1 week after the 10 bite, all of whom were referred for surgical debridement. One patient developed a healing contracture of the forearm which necessitated surgical release. Healing occurred by secondary intention over several months following the bites.

Seven consecutive bites occurring in 5 patients were treated with imiquimod. These cases are summarized in the Table below. Presenting signs and symptoms were 15 consistent with those recorded for patients treated by conventional means. Tenderness or pain, with erythema, characteristic blanching and firm induration were present in every case. In one case (L.S.), punctuate marks were noted at the center of the indurated area. Pain relief was reported by all patients within 1-2 days following the first dose of imiquimod. Marked improvement in both induration and erythema was noted by day 7, 20 with full resolution in all but one case by day 14. In patient Y.C., erythema was noted to be cleared at the day 7 visit but developed again by day 14. The reappearance of erythema is presumed to be secondary to imiquimod.

Patients C.R. and L.S. each sustained two bites. In the case of L.S., the first bite was resolved 9 days after it occurred. The second bite occurred 16 days after the first bite 25 and resolved completely, with treatment, by the 5th day. The difference in clinical course may have been due to differences in the age of the spider, the sex of the spider (females inject greater volumes of venom), or an acquired immunity following the first bite. Necrosis did not develop in any of the imiquimod treated cases. No residual scarring or pigmentation changes were noted at the day 28 follow-up visit.

30 The probability of observing 0 out of 7 consecutive cases with no necrosis, given the underlying historical rate of 7/12 (0.583), is quite low based on a binomial probability distribution ($p=0.002$) or a Chi-square analysis ($p=0.01$).

Summary of Cases				
Patient/Age/Sex	Bite Location	Presentation	7 Day Follow-up	14 Day Follow-up
R.M/ 39y/ M	Right calf	1.5 cm induration 9 cm erythema Painful	0.5 cm induration No erythema No pain or tenderness	Completely healed
R.H/ 45y/ M	Right calf	1.3 cm induration 10 cm erythema Very painful	1.25 cm firm induration 5 cm induration Non-tender	Completely healed
L.S./ 28y/ F	Right thigh	1.5 cm induration 7.5 x 11 cm erythema Tender	2.5 cm central core No erythema No pain or tenderness	Completely healed
L.S./ 28y/ F	Left buttock	1.0 cm induration Erythema Painful	Completely healed	
C.R./ 35y/ F	Left thigh	1.0 cm central core 6.0 cm erythema Painful	0.5 cm central core 2.0 cm erythema	Completely healed
C.R./ 35y/ F	Right breast	1.2 cm central core 3.0 cm erythema Painful	1.0 cm central core No erythema	Completely healed
Y.C./ 35y/ F	Right calf	1.8 cm central core 1.2 cm erythema Painful	0.75 cm ulcer No erythema Decreased pain	Ulcer healed Erythema present (Erythema resolved by d28)

WHAT IS CLAIMED IS:

1. A method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion.

10

2. The method of Claim 1 wherein the immune response modifier compound is a compound of Formula I



I

wherein

15 R₁ is selected from the group consisting of S and NR₃,

R₂ is selected from the group consisting of hydrogen, straight and branched chain alkyl containing one to six carbon atoms, and alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms; and

20 R₃ is selected from the group consisting of straight and branched chain alkyl containing one to six carbon atoms and straight or branched chain hydroxy alkyl containing one to six carbon atoms; or a pharmaceutically acceptable salt thereof.

3. The method of Claim 2 wherein R₁ is NR₃.

25

4. The method of Claim 2 wherein R₁ is S.

5. The method of Claim 2 wherein R₂ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, and ethoxymethyl.
6. The method of Claim 2 wherein R₃ is selected from the group consisting of 2-methylpropyl and 2-hydroxy-2-methylpropyl.
7. The method of Claim 2 wherein the IRM compound is selected from the group consisting of 4-amino-2-ethoxymethyl- α,α -dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 2-methylthiazolo[4,5-*c*]quinolin-4-amine, 2-ethylthiazolo[4,5-*c*]quinolin-4-amine, 2-propylthiazolo[4,5-*c*]quinolin-4-amine and 2-butylthiazolo[4,5-*c*]quinolin-4-amine.
8. The method of Claim 1 wherein the immune response modifier compound is applied via a cream or a gel.
- 15 9. The method of Claim 1 wherein the source of the envenomation is an arthropod.
10. The method of Claim 9 wherein the arthropod is a spider.
- 20 11. The method of Claim 9 wherein the arthropod is an insect of the order Hymenoptera.
12. The method of Claim 1 wherein the source of envenomation is a marine animal.
- 25 13. The method of Claim 12 wherein the marine animal is a jellyfish.
14. A method of preventing dermonecrosis caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline

amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the envenomation.

15. The method of Claim 14 wherein the immune response modifier compound is a
5 compound of Formula I



wherein

R₁ is selected from the group consisting of S and NR₃,

R₂ is selected from the group consisting of hydrogen, straight and branched chain
10 alkyl containing one to six carbon atoms, and alkoxyalkyl wherein the alkoxy moiety
contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms;
and

R₃ is selected from the group consisting of straight and branched chain alkyl
containing one to six carbon atoms and straight or branched chain hydroxy alkyl
15 containing one to six carbon atoms; or a pharmaceutically acceptable salt thereof.

16. The method of Claim 15 wherein R₁ is NR₃.

17. The method of Claim 15 wherein R₁ is S.

20 18. The method of Claim 15 wherein R₂ is selected from the group consisting of
hydrogen, methyl, ethyl, propyl, butyl, and ethoxymethyl.

19. The method of Claim 15 wherein R₃ is selected from the group consisting of 2-
25 methylpropyl and 2-hydroxy-2-methylpropyl.

20. The method of Claim 15 wherein the IRM compound is selected from the group
consisting of 4-amino-2-ethoxymethyl-*a,a*-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-

ethanol, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 2-methylthiazolo[4,5-*c*]quinolin-4-amine, 2-ethylthiazolo[4,5-*c*]quinolin-4-amine, 2-propylthiazolo[4,5-*c*]quinolin-4-amine and 2-butylthiazolo[4,5-*c*]quinolin-4-amine.

- 5 21. The method of Claim 14 wherein the immune response modifier compound is applied via a cream or a gel.
22. The method of Claim 14 wherein the source of the envenomation is an arthropod.
- 10 23. The method of Claim 22 wherein the arthropod is a spider.
24. The method of Claim 22 wherein the arthropod is an insect of the order Hymenoptera.
- 15 25. The method of Claim 14 wherein the source of envenomation is a marine animal.
26. The method of Claim 25 wherein the marine animal is a jellyfish.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 October 2001 (11.10.2001)

PCT

(10) International Publication Number
WO 01/74343 A3

(51) International Patent Classification⁷: A61K 31/4745. (81) Designated States (national): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(21) International Application Number: PCT/US01/10291

(22) International Filing Date: 30 March 2001 (30.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/193,120 30 March 2000 (30.03.2000) US
09/820,420 29 March 2001 (29.03.2001) US

(71) Applicant: 3M INNOVATIVE PROPERTIES COMPANY [US/US]; 3M Center, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(72) Inventor: SLADE, Herbert B.; Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(74) Agents: HOWARD, Mary Susan et al.; Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
7 February 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/74343 A3

(54) Title: METHOD FOR THE TREATMENT OF DERMAL LESIONS CAUSED BY ENVENOMATION

(57) Abstract: A method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion is disclosed.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/10291

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4745 A61K31/429

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 20847 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 28 October 1993 (1993-10-28) cited in the application the whole document	2-7, 15-20
A	WO 00 06577 A (3M INNOVATIVE PROPERTIES CO.) 10 February 2000 (2000-02-10) cited in the application the whole document	2-7, 15-20
A	US 5 389 640 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 14 February 1995 (1995-02-14) cited in the application the whole document	2-7, 15-20

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *S* document member of the same patent family

Date of the actual completion of the international search

19 October 2001

Date of mailing of the international search report

31/10/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5816 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

Economou, D

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,8-14,21-26

Present claims 1,8-14,21-26 relate to an extremely large number of possible compounds/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds/methods disclosed in claims 2-7 and 15-20.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/10291

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9320847	A 28-10-1993	AT 142110 T		15-09-1996
		AU 674313 B2		19-12-1996
		AU 4048093 A		18-11-1993
		DE 69304521 D1		10-10-1996
		DE 69304521 T2		20-02-1997
		DK 636031 T3		24-02-1997
		EP 0636031 A1		01-02-1995
		ES 2092306 T3		16-11-1996
		HK 1007962 A1		30-04-1999
		HU 69993 A2		28-09-1995
		HU 9500752 A3		28-11-1995
		IL 105325 A		14-11-1996
		JP 7505883 T		29-06-1995
		KR 263804 B1		16-08-2000
		MX 9302199 A1		31-08-1994
		NO 943920 A		14-10-1994
		NZ 252020 A		21-12-1995
		NZ 280098 A		26-06-1998
		WO 9320847 A1		28-10-1993
		US 6083505 A		04-07-2000
		ZA 9302627 A		14-10-1994
WO 0006577	A 10-02-2000	US 6110929 A		29-08-2000
		AU 5133199 A		21-02-2000
		EP 1100802 A1		23-05-2001
		NO 20010497 A		27-03-2001
		WO 0006577 A1		10-02-2000
US 5389640	A 14-02-1995	US 5977366 A		02-11-1999
		US 5605899 A		25-02-1997
		US 5741909 A		21-04-1998
		AT 179711 T		15-05-1999
		AU 658621 B2		27-04-1995
		AU 1566992 A		06-10-1992
		AU 673309 B2		31-10-1996
		AU 2715795 A		21-09-1995
		CA 2104782 A1		02-09-1992
		CZ 9301788 A3		18-10-1995
		DE 69229114 D1		10-06-1999
		DE 69229114 T2		04-11-1999
		DK 582581 T3		08-11-1999
		EP 0582581 A1		16-02-1994
		EP 0872478 A2		21-10-1998
		ES 2131070 T3		16-07-1999
		HU 67026 A2		30-01-1995
		HU 211242 B3		28-11-1995
		IE 920605 A1		09-09-1992
		IL 101110 A		08-12-1995
		IL 114570 A		31-10-1996
		JP 2955019 B2		04-10-1999
		JP 6504789 T		02-06-1994
		KR 235389 B1		15-12-1999
		NO 933069 A		01-11-1993
		NZ 241784 A		27-06-1995
		SG 46492 A1		20-02-1998
		SG 70625 A1		22-02-2000
		WO 9215582 A1		17-09-1992
		ZA 9201540 A		25-11-1992